PB-237 738-T

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1974

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PB 237 738-T

APTIC 49913 EPA-TR 98-73

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[Rol' Mikroelementov v Krovotvorenii]

Terapevticheskiy Arkhiv, Vol. 35, December 1963, pp. 3-14.

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NATIONAL TECHNICAL
INFORMATION SERVICE
U S Department of Commerce
Springfield VA 22151

Translated for APTIC by
Translation Consultants, Ltd., Arlington, Virginia

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ROLE OF TRACE ELEMENTS IN BLOOD FORMATION

Trace elements (biotics) have a high biological activity and a well-expressed catalytic effect. There is a close correlation between them, enzymes, hormones and vitamins. Trace elements either enter directly into the structure of enzymes or in the form of compounds are responsible for their activation.

The biological activity of elements is determined by what place they occupy in the D. I. Mendeleyev periodic system. Investigations by a number of scientists have established the participation of elements in the fourth period (horizontal row) in the hemopoietic process; this can be represented in the form of the series: Ti < V < Cr < Mn < Fe, Co, Ni, Cu > Zn > Ga > Ge > As. The most active are the intermediate elements - manganese, iron (macroelement), cobalt, nickel and copper. Each of them acts on different hemopoietic links, supplementing one another. Cobalt facilitates the new formation of reticulocytes and the utilization of reserve iron. Nickel acts like cobalt. Copper participates in the synthesis of hemoglobin. Manganese accelerates the maturing of erythrocytes.

In different forms of anemias, especially iron-refractory, a positive therapeutic effect can be obtained from the administration of hemostimulators from among the trace elements.

In this review of the literature we present facts obtained under

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experimental and clinical conditions, theoretical generalizations and practical recommendations.

Cobalt. Participation of this microelement in blood formation is the most important and interesting aspect of its biological role.

In 1879 Azary for the first time described the influence of cobalt on the blood-forming organs, observing primarily its toxic effect. Somewhat later Pittini and Messina established that as a result of adding salts of this microelement to the food ration of rats they exhibited onset of cobalt-induced true polycythemia. These investigations were completely forgotten and only in 1930 did Waltner again "discover" that cobalt, added to the food, causes hyperplasia of the red bone marrow, increasing the hemoglobin level by 30-40 units and the number of erythrocytes by four million, with a preceding reticulocytic wave. When the administration of cobalt stopped the blood picture returns to the initial state after 20-40 days.

Polycythemia arises as a result of the stimulating effect of the microelement on the rate of formation of erythrocytes, more rapid maturing of basophilic normoblasts and the entry of mature erythrocytes in the circulating blood, and not on the lifetime of the erythrocytes. The development of cobalt-induced polycythemia is accompanied by an increase in the quantity of globin and hematin. A favorable effect of the microelement on the synthesis hemoglobin and an increase in the number of reticulocytes and erythrocytes has been established in many species of animals.

The effect of cobalt on hemopoiesis is effective if the body has adequate reserves of iron and copper. The physiological activity of

cobalt is reduced after interaction with amino acids containing sulfur; this is evidently dependent on the formation of less active complexes (L. O. Voynar).

According to the hypothesis formulated by Orten, Laforet and Wolff, the microelement acts directly on the brain, thereby stimulating hemopoiesis. At the same time, cobalt administered into the body causes partial hemolysis, whose products, in the opinion of these authors, are also stimuli of the blood-forming apparatus. As a result, reticulocytosis appears, followed by an increase in the number of erythrocytes, and there is an increase in the hemoglobin level.

Weissbecker feels that the microelement causes a two-phase polyglobulia: first (after 24 hours) there is a mobilization of formed elements from the blood depots and then (after three to seven days) a true erythroformation and an increase in the hemoglobin level. Cobalt as a cation evidently does not penetrate into the forming erythrocytes, but is capable of entering into the composition of the hemoglobin during its formation. The affinity of the microelement to the sulfhydryl groups is more clearly expressed than for iron and therefore the elimination of the latter from its compounds is possible. Data are also available indicating that cobalt is capable of depressing tissue respiration, including respiration of bone marrow cells, as a result of which a compensatory polycythemia develops (Barron, Greif, Kretschmer).

However, not in all cases of administration of cobalt salts does one observe indications of hypoxia of bone marrow tissue, although hyperplasia of the erythroblastic elements may occur in the bone marrow. In the

experimental animals consuming cobalt chloride, in addition to the development of polycythemia there is an increase in the activity of blood serum cholinesterase. Accordingly, it is assumed that stimulation of erythropoiesis transpires by means of an increase in the activity of this enzyme.

Berlin mentions a concentration of radioactive cobalt in the bone marrow during polycythemia and the biological activity of the microelement is manifested most completely in this blood-forming organ. It was established that cobalt accumulation in the bone marrow occurs parallel with an increase in the number of erythrocytes and an increase in the hemoglobin level in the peripheral blood. As a result of prolonged administration of the microelement the fatty tissue in the bone marrow is replaced by completely hemopoietic tissue and there is a considerable increase in the number of normoblasts. In the blood serum there is a decrease in the content of inorganic iron, which is attributable to its increased use during the synthesis of hemoglobin in the bone marrow. A new rise in serum iron and a simultaneous decrease in the level of this metal in the reticulohistiocytic system during anemias indicate its possible mobilization under the influence of cobalt.

Thus, cobalt improves the use of iron, favoring the penetration of its atom into the hemoglobin molecule. Under the influence of the microelement there is also an increase in the absorption of iron in the intestine, as is indicated by a decrease in the ferritin content in its mucous membrane.

Cobalt actively participates already in embryonal blood formation. Already from 12 weeks of interuterine development, with the appearance of blood formation, the microelement is determined in the diaphyseal centers

of blood formation. During the fifth month of intrauterine development, when megaloblastic blood formation is replaced by normoblastic blood formation, cobalt is accumulated in the liver.

Goldwasser feels that the microelement stimulates the formation of erythropoietin. The author believes that the hemopoietic effect does not arise due to the direct effect of cobalt, present in the plasma, but due to stimulation of the formation of erythropoietin. Hydrocortisone intensifies the effect of the microelement, which is attributable to the synergism of humoral factors: a hormone and erythropoietin (Fischer).

Many investigators, as a result of discovery and study of vitamin B_{12} (cyanocobalamin), are inclined to attribute the participation of cobalt in blood formation not to its independent activity, but to the increased formation of an antianemic vitamin and the effect of this vitamin on the bone marrow, particularly since the activity of the cobalt ion in vitamin B_{12} is greater by a factor of 1,000. In the vitamin molecule the microelement evidently plays the same role as iron ion in the hemoglobin molecule, that is, it is the active substance of the molecule.

An evaluation of the therapeutic effect of cobalt chloride and vitamin B_{12} during experimental anemias revealed that cobalt chloride is considerably more effective in the case of hypochromic microcytic anemia, whereas vitamin B_{12} is more effective in the case of hyperchromic macrocytic anemia.

Cobalt must be regarded as an independent stimulus of the blood-forming tissue (Wolff). At present it is customary to assume that this microelement and its organometallic compounds are powerful stimulators of hemopoiesis.

According to data published by a number of researchers, in the blood of adult human subjects, cobalt is detected in these quantities: 8.0-16.6 γ % (I. N. Usov), 6.2±0.5 γ % (I. S. Gul'ko), 10.8±3.1 γ % (V. Ya. Shustov), 4.8±0.3 γ % (L. I. Idel'son and Ye. D. Zhukovskaya), 0.4-6.3 γ % (Koch, et al). The nonuniformity of the indices can be attributed to the diversity of the existing methods (some of them give exaggerated results) and to the difference in biogeochemical processes. There is a fluctuation in the cobalt level in the human blood during the course of the day and also in dependence on season of the year. In autumn, due to the consumption of fresh vegetables and fruits rich in mineral substances, including cobalt, its level in the blood is somewhat higher. The content of this microelement in the bone marrow and liver is greater than in the blood on the average by a factor of 1 1/2 - 2.

An exogenous inadequacy of this microelement in man is unknown to us, other than for macrocytic anemia in residents of the Black Forest mountain region in West Germany, whose drinking water is poor in cobalt.

In a normally transpiring pregnancy the quantity of cobalt in the blood is reduced. However, this decrease does not exceed physiological limits and is only a result of the increased need of the fetus for this microelement (G. V. Asmolovskiy). In the case of blood loss and toxicosis the cobalt level in the blood of women is considerably reduced, whereas the consumption by the fetus of this element continues to increase. Accordingly, a deficit of the trace element in the mother's body can arise, and this can cause the development of anemia in the newborn child and mother.

Interesting data have been obtained in a study of the cobalt level in the blood and blood-forming organs of victims of anemias and leukoses. In most victims of Biermer's anemia, in the recidivation phase the quantity of the trace element in the whole blood was reduced; only in a few cases was its initial level high. There is a direct dependence between the degree of anemia and the cobalt level in the blood. A postmortem study of the bone marrow and liver revealed an appreciable decrease in the reserves of the trace element in these organs in Biermer's anemia. In this same form of anemia, but with a moderate decrease in the red blood indices, there was an increase in the cobalt content in the erythrocytes, as well as a dependence between those changes and the color index (V. Ya. Shustov, A. S. Zaytseva, Heyrovsky). In the course of treatment of patients there is a tendency to normalization of the level of the trace element in the blood; this can undoubtedly characterize the dynamics of the blood-forming process. All this indicates a cobalt inadequacy in Biermer's anemia.

In posthemmorhagic, carcinogenic and chloranemia there is also an impairment in the cobalt level in the blood and in the blood-forming organs, but to a lesser degree. There are indications of a decrease in the level of the trace element in the blood of children during hypochromic anemia of infectious-alimentary origin (O. M. Lago).

Acute leukemia, chronic lympholeukosis and myeloma are accompanied in most cases by a low concentration of the trace element in the blood, but chronic myeloleukosis and lymphogranulomatosis - by a high concentration. With the onset of clinical - hematological remission one notes a tendency to normalization of the cobalt level. Further progress of the disease leads

to a more conspicuous decrease in the blood cobalt level, which is especially well expressed during the terminal period (L. V. Vologo, V. Ya. Shustov). In the bone marrow, parallel with the development of a myeloproliferative process, there is an increase in the cobalt quantity (M. P. Pavlova). In the case of hypoplasia and aplasia of bone marrow one usually observes a considerable decrease of cobalt in the blood and its disappearance in the blood-forming organs. These observations coincide with an indication of a marked decrease in the natural radiation of ash of tubular bones in this same pathological state.

Change in the content of trace elements, together with other factors, is of considerable importance in the formation of radiation pathology. Already in the early stages of development of radiation sickness there are considerable impairments in cobalt content in the organs and tissues, a redistribution of the metal, an increase in its elimination in the urine, and in the last analysis a decrease in the total quantity of the trace element in the body. An endogenous cobalt deficit is created; this is directly related to an impairment in blood formation during radiation damage.

Copper. Already in the early stages of embryonal development copper partic.pates in blood formation, as is indicated by its considerable accumulation in the liver of the fetus where a hemopoietic process transpires at this time. Observation of rats consuming a whole milk diet poor in copper revealed a rapid development of anemia. Iron in this case did not exert antianemic effect; after copper was added there was a normalization of the hemoglobin level over a period of one or two weeks.

Some authors feel that chemically pure iron exerts a week therapeutic effect if it is not "contaminated" by copper, that is, the trace element in a unique "conductor" of the macroelement (Hart). In the case of an inadequacy of the first in the diet of the animals there is a decrease in the absorption of the second from the gastrointestinal tract and its mobilization from the tissues and utilization in the bone marrow is impaired. Due to the ratio of iron to copper 50:1 the speedy synthesis of hemoglobin in the body is ensured.

In order to clarify the specific nature of the blood-forming effect of copper we added to the food ration of anemic rats not only iron, but the salts of different metals: zinc, manganese, nickel, chromium and other trace elements. It was found that only copper has a specific effect on blood formation (Elvehjem).

Experiments with a radioactive isotope of this trace element revealed that in anemic rats radioactive copper penetrates more rapidly into the bone marrow and is retained there a considerably longer time. It can therefore be assumed that the entry of the trace element into the erythrocytes occurs where the hemoglobin synthesis process occurs, that is, in the bone marrow.

Copper participates in creating an intermediate hemoglobin compound. Iron-copper-nucleoprotein complexes which are hemoglobin precursors have been described (L. F. Dmitriyenko). Not entering into the composition of the blood pigment molecule itself in higher animals and man, copper in biotic concentrations specifically catalyzes the introduction of iron into the hemastructure and therefore is an irreplaceable activator of hemoglobin

formation. In order to eliminate hypochromia it is sufficient to introduce into the body the very minimum quantities of the microelement in combination with iron.

The favorable effects of copper on erythropoiesis can also be attributed to its influence on cytochromoxidase, catalase, cell respiration and an increase in the oxygen capacity of the blood (A. O. Voynar).

It was experimentally established that with the injection of copper parenterally into the bone marrow there will be a hyperplasia of the basophilic normoblasts. In the case of an inadequacy of the trace element in the body the lifetime of the erythrocytes is reduced and there is a decrease in the area of blood formation in the bone marrow, so that anemia develops (Bush). In the case of phenylhydrazine anemia the copper content in the blood of animals doubles in comparison with the normal level. At the same time there is an exceedingly marked decrease in the copper concentration in the liver and bone marrow. During the recovery of the animals, in addition to an increase in the number of erythrocytes and quantity of hemoglobin there is a gradual decrease in the level of the trace element in the blood and an increase in the blood-formation organs.

According to data published by a number of researchers, the blood of adult human beings has the following copper content: 185±8.2 γ % (V. Ya. Shustov), 187±6 γ % (M. M. Korobenkova), 113±12 γ % (A. S. Zaytseva), 108±12 γ % (I. S. Gul'ko), 98±12 γ % (Gubler). It is distributed approximately uniformly among the formed elements and plasma. In the erythrocytes the trace element forms a stable compound with albuminas (hemocuprein), and in the plasma with α_2-globulins (peruloplasmin),

constituting an important link in the chain of copper metabolism and hemoglobin synthesis. The liver contains an average of about 700 γ % of the trace element, for the most part in a compound with protein (hepatocuprein).

During the day there are rhythmic fluctuations in the blood ("diurnal rhythm"). In the morning its level is maximum; after midday it begins to drop off and at nighttime attains minimum levels. There is also a change in the quantity of the trace element in relation to season of the year.

The ovarian-menstrual cycle in women is also accompanied by a fluctuation in the level of this trace element. In the case of a normally transpiring pregnancy, beginning with the third month there is an increase in its content in the blood. A return to normal levels occurs during the several months after birth. During the pregnancy period there is a migration of copper (cuproprotein) from the mother's liver into the blood-forming organs of the fetus. At the same time the absorption of the trace element into the intestine is impaired and there is a considerable increase in its elimination with the urine (M. G. Mirzakarimov). As a result, a copper deficit appears in the body and with the inadequate receipt of the trace element in the food the pregnant mothers develop anemia. During the lactation period, especially during the first months, the new mothers who are nursing systematically lose copper. That is why during the postnatal period women can develop hypomicroelementosis, when even small losses of blood are accompanied by a severe form of anemia.

The copper reserve with which the childern are born is limited. At

the age of four or five months a child, particularly if not nursed naturally, experiences a shortage of the trace element because the mother's milk, much less cow's milk, is poor in copper and cannot meet the increasing needs of the child's body. A shortage of copper in combination with hypoferremia and hypoproteinemia favors the development of alimentary hypochromic anemia. In alimentary anemia in childhood a hyper- and hypocupremia is observed (O. M. Lago, L. P. Bushmeleva): in cases of infectious anemia it is more common to observe hypercupremia as a result of impairment in the assimilation of copper and inhibition of bone marrow functioning.

There are a considerable number of investigations of the copper level in the blood and blood-forming organs in adult persons suffering from anemia and leukoses. In posthemorrhagic and gastrogenic iron-deficiency anemia and Biermer's anemia in most cases there is an increase in the copper level in the whole blood, erythrocytes and blood serum and also a change in the coefficient of the distribution of this trace element between the formed elements and the serum. In the course of treatment, beginning with the period of the reticulocytic crisis, parallel with an improvement in the general condition of the patient, regeneration of bone marrow blood formation and an increase in the number of erythrocytes and the quantity of hemoglobin, there is a decrease (normalization) in the level of the trace element (Sh. B. Babayev, Yu. V. Chichua, A. S. Zaytseva, V. Ya. Shustov, Varghelovici, et al.). In subjects dying from different forms of anemia it is possible to observe an impoverishment of the liver and bone marrow with copper. In chronic anemia, when the disease has persisted for a long time, especially when it acquires a hyporegenerative nature, the copper content in the blood

is relatively low. There is evidently a gradual exhaustion of reserves of the trace element and a time comes when even with a considerable degree of anemia no hypercupremia occurs. As an example of a decrease in the copper level in the blood and blood-forming elements one can mention hypoplastic anemia.

An objective index of the deficit of this trace element is the degree of the body saturation with it. In healthy individuals after the daily administration of 6-8 mg of copper an equilibrium in the balance of the microelement sets in after three or four days. At the same time, in the case of a severe degree of anemia, due to the considerably greater need for it and its increased elimination with the urine, such an equilibrium sets in only on the 20th-25th day. Thus, there is a correlation between the rate of body saturation with copper and the gravity of the anemia.

In most patients with different forms of acute and chronic leukoses, particularly during the period of development of anemia, one can also observe an increase in the copper level in the blood to some degree (R. G. Kapran, K. V. Nikulin, V. Ya. Shustov, Gubler, Rechenberger). In lymphogranulematosis hypercupremia serves as one of the indicators of activity and progress of the disease. "Spontaneous" or therapeutic remission is characterized by a considerable decrease in the concentration of this metal in the plasma, which frequently precedes normalization of temperature, the erythrosedimentation rate and the number of leukocytes and erythrocytes (Pagliardi). The established shifts in the content of the trace element in the body must be examined in relation to the prevailing impairment of blood formation in leukoses.

It is primarily the ionic form of copper which accumulates in the blood of patients; this evidently occurs through a mobilization of the reserves of the trace element from the organs of deposition. Most researchers are inclined to consider the increase in the concentration of the trace element in the blood during anemic states to be a compensatory body reaction in response to the developing "copper starvation." Administration to the trace element for therapeutic purposes causes a decrease in hypercupremia (M. G. Mirzakarimov, V. Ya. Shustov, Gubler). As the anemia decreases the need for iron drops off. The systems stimulating its assimilation in this case become less active. Since copper is associated precisely with these systems, its level naturally decreases. However, a shortage of copper in the liver cannot but be reflected in its functioning, and especially in its capacity for synthesizing copper-protein compounds. The catalytic activity of ionic copper is lower than that of the copper-protein complex. In the case of anemia and leukoses this can lead to an impairment of the activity of enzymatic systems (cytochromoxidase, etc.), in whose makeup the trace element enters as an irreplaceable metal component. In this connection it is not without interest to note that the liver, deprived of copper, does not exert an antianemic effect in experiments.

In the early stages of radiation disease and especially during its height there is an increase in the copper level in the blood and elimination of the microelement with the urine, its concentration in the organs changes, followed by a redistribution of the metal. Prior to the death of the animals the concentration of the trace element in the blood and blood-forming organs is reduced. This dynamics of the content of copper in the body evidently must be examined in relation to the period in the course of

radiation sickness or as a "manifestation of compensatory-protective mechanisms or as a result of developing disaggregation of chemical processes in the tissues which leads the body to death" (G. A. Babenko).

Manganese. This trace element in small doses in anemic animals causes an increase in the number of polychromatophilic normoblasts and erythrocytes and an increase in the quantity of circulating blood, as well as a rise in the hemoglobin level. The administration of large doses of manganese over a long period of time led to exhaustion of the blood-forming organs and a decrease in the red blood indices. The development of progressive anemia and slowing of restoration of the composition of the red blood after blood loss can be observed in some animals with an inadequate content of the trace element under normal conditions.

It has been noted that in persons directly in contact with manganese dust prior to the period of intoxication there is an increase in the percentage of hemoglobin and the number of erythrocytes (V. S. Surat, et al.). According to observations made by Falyudi, administration of a protein compound of manganese to subjects afflicted with anemia increases the number of erythrocytes and quantity of hemoglobin in the blood. Participation of the trace elements in the hemopoietic process also is demonstrated by the selective accumulation of manganese in the liver of the fetus in the 12th to the 25th week (G. G. Gatsko).

In the animal body there is probably a definite relationship between manganese and copper metabolism, necessary for blood-formation processes. Manganese in the corresponding doses exerts an influence on the assimilation of copper by the body. Their simultaneous administration leads to a

considerable increase in the total content of copper and a relative increase in its concentration in the blood, liver and bone marrow. At the same time, in the development of anemia caused by an inadequacy of copper in the food ration, parallel with a decrease in this trace element in the liver of animals there is also a decrease in the manganese content. With the entry of both trace elements into the body it is more likely that the red blood indices will be restored. Accordingly, one element can exert an influence on metabolism of the other and in this way exert its biological effect. A definite correlation was established between manganese and erythrocytes, with their heminic fraction.

Experiments with a radioactive isotope of manganese revealed that it enters into erythrocytes. The microelement is possibly related to the synthesis of porphyrins.

However, some researchers dispute the favorable effect of manganese on the blood-formation process. For example, Krauss did not observe an improvement in the alimentary anemia of rats when the trace element was added to the food ration in combination with iron, whereas Petronio and Gasirola did not detect in these victims of hypochromic anemia any dependence between the content of manganese and the hemoglobin level.

In all probability the influence of the trace element on blood formation processes is nonspecific, related to its high oxidability. The favorable effect obtained with the addition of manganese to iron is manifested only in combination with the effect of cobalt and copper, biotics specifically exerting an influence on blood formation.

According to data published by a number of researchers, the human blood contains manganese in these quantities: 12.0±3.6 γ % (I. S. Gul'ko), 13.3±6.2 γ % (V. Ya. Shustov), 14.0±0.04 γ % (G. G. Gatsko), 2-15 γ % (Kehoy and Cholak); in the erythrocytes there is two or three times more manganese than in plasma. In the blood the trace element is found in the form of a compound with protein. The liver contains 100 γ % of manganese (N. F. Volkov).

During a period of pregnancy the quantity of the trace element in the blood is somewhat increased (G. G. Gatsko), whereas in the liver it is decreased; its elimination in the urine is intensified. In women during this period in addition to a shortage of cobalt and copper the body also exhibits a relative manganese inadequacy. This hypo-Co-, Cu-, Mn-microelementosis creates conditions for the appearance of anemia in pregnant women, new mothers and nursing babies.

In different forms of anemia, in the blood in most cases parallel with the gravity of the disease one can observe a decrease in the manganese level. In the process of antianemic therapy there is a tendency to its normalization. In a post-mortem study of the bone marrow and liver one can detect a decrease in the reverse of the trace elements in these organs. In leukoses and other systemic blood diseases one also observes a considerable deviation from the normal manganese level in the blood. Acute leukosis and myelomatosis are accompanied most frequently by its high concentration, but lymphogranulematosis,

chronic lympho- and myeloleukosis and aplastic anemia are accompanied by a low concentration (V. Y. Shustov).

V. A. Leonov feels that the atomic decay of natural radioactive macro- and microelements, concentrated in the bones, supplies the energy for blood formation. The author feels that the main link in the pathogenesis of leukoses is evidently an impairment in the metabolism of a complex of natural radioactive elements and in turn - microelements. According to this hypothesis, it is also possible that cobalt, copper and manganese (radioactive and nonradioactive), having the most clearly expressed hemostimulating properties, play a significant note in the chain of these impairments in myeloproliferative diseases.

Nickel resembles cobalt in its physiological effect, and in particular, in its influence on blood formation. In experimental posthemorrhagic anemia in animals the subcutaneous injection of compounds of the trace elements favors an acceleration of the regeneration of erythrocytes (N. B. Nasel'skiy, Caso). It exerts a lesser effect on the level of hemoglobin and iron in the blood plasma. The intraperitoneal injection of nickel chloride in guinea pigs causes them to exhibit polycythemia, macrocytosis and leukocytosis. The administration of nickel salts to donors in a dose of 5 mg per day accelerates the regeneration of erythrocytes and hemoglobin (M. Mil' and K. A. Meshcherskaya-Shteynberg).

This trace element is constantly present in the blood and blood-forming organs. Its content in the whole blood varies in the range 10-40 γ % and and in the bone marrow in the range 50-120 γ % (L. V. Volod'ko, I. S. Gul'ko, I. N. Usov). In leukoses the nickel concentration in the blood and

blood-forming organs increases, but in different forms of anemia it decreases. There is a definite dependence between the degree of anemia and quantitative changes in the trace element. In most cases changes in the blood concentration of nickel and cobalt and also their dynamics are similar during the period of antianemic therapy. With the administration of cobalt or injection of its preparations, vitamin B_{12} and coamide, there is an increase in the level not only of the trace element administered for therapeutic purposes, but also of "affine" nickel (V. A. Leonov, V. Ya. Shustov).

The matter of the participation of zinc in blood-formation processes remains unsolved. A number of authors feel that it exerts an influence on hemopoiesis. The daily addition of the trace element to the food considerably accelerated the regeneration of hemoglobin and erythrocytes in animals with experimental anemia. Later, however, it was found that the experiments were conducted with insufficiently pure preparations of zinc containing copper and other trace elements. The detection of porphyrins, containing zinc, in the urine gives basis for assuming the participation of this trace element in the forming of compounds of a heminic nature.

The blood contains from 600 to 900 γ % of zinc. Most of it is concentrated in the erythrocytes; its high concentration in eosinophils is characteristic. The trace element, present in plasma, is bound with transferrin, which thus causes migration of both iron and zinc (A. O. Voynar, Vallee, Wolff).

Investigations made using radioactive zinc show that erythrocytes and bone marrow accumulate Zn^{65} in a considerable quantity. The high level of this trace element in the erythrocytes is attributable to a considerable concentration of a metalloenzyme, carboanhydrase, containing zinc as the

specific metal in them. There is a direct dependence between the activity of the enzyme and the content of the trace element in the erythrocytes. During hypoxia and hypochromic anemia there is a migration of the zinc from the plasma into the erythrocytes and an increase in the content of carboanhydrase and an intensification of its activity; this favors a more intensive absorption of oxygen under hypoxemic conditions. Accordingly, in tissue respiration processes the enzyme plays an equally important biological role as hemoglobin, whereas zinc in its participation in these processes is equally important as iron.

In patients with achylous chloranemia there is a decrease in serum zinc which is evidently associated with an impairment in the absorption of the trace element in the intestine. In diseases accompanied by hemolysis, with an acute radiation syndrome, the zinc content in the serum increases. A considerable increase in the quantity of the trace element in the whole blood and especially in the erythrocytes is observed in most victims of Biermer's anemia. An increase in the concentration of the trace element in the erythrocytes can be regarded as a compensatory-adaptive body reaction to oxygen starvation.

In leukoses the leukocytes contain only 10% of the normal quantity of zinc; this is possibly dependent on their differentiation (Dennes, Gubler). During this period of therapeutic remission the concentration of leukocytic zinc is normalized. A dependence between the number of leukocytes and the level of the trace element in them is observed only in patients with chronic lympholeukosis.

At the present time there is little direct evidence of an antianemic

effect of zinc; however, taking into account the position occupied by the microelement in the "iron group" in the periodic system, researchers rightly postulate its participation in blood-formation processes.

The hemostimulating effect of vanadium, titanium, chromium and germanium is caused by blocking of the redox system of hydrogen carriers; this results in hypoxemia and irritation of the bone marrow (A. O. Voynar). Vanadium gluconate used in experiments causes an increase in the number of reticulocytes and erythrocytes and an increase in the hemoglobin level. In posthemorrhagic anemia the trace element accelerates the process of regeneration of red blood in patients. The addition of titanium sulfate to the daily ration of donors repeatedly furnishing blood somewhat increases the number of erythrocytes. The testing of the effect of compounds of this trace element on hemopoiesis in anemic animals yielded extremely contradictory data requiring further study.

The literature contains individual observations indicating a positive effect of chromium and germanium on the formation of hemoglobin and erythrocytes (A. O. Voynar, Beard). Arsenic in microdoses can favor an increase in the number of erythrocytes in victims of anemia. Its prolonged use leads to hemolysis. In combination with copper, manganese and iron, arsenic increases the hemoglobin level in experiment animals (Skinner). As a cytostatic substance this microelement in the form of Fowler's solution was used for a long time in hematological practice for treating patients with chronic lympholeukosis.

Use of cobalt, copper and manganese for treating victims of anemia. At the basis of treatment with microelements is their use in approximately those physiological (biotic) concentrations in which they are found in the body itself. Metallic cobalt and its salts were used for the first time in treating children ill with secondary anemia. Later the trace element was prescribed for anemia associated with pulmonary tuberculosis, rheumocarditis, chronic suppurative infections, blood loss, helminthism and leukoses during a period of three to four weeks. A reticulocytic crisis appeared on the seventh to tenth day from onset of treatment, followed by an increase in the number of erythrocytes, and the hemoglobin level increased.

A side effect of cobalt was sometimes manifested in nausea and reddening of the face so that it was necessary to stop the initiated treatment. Cobalt sulfate in daily doses of 10-50 mg (scaled to pure metal) was used in treating victims of macrocytic anemia refractory to iron (Bush, Trummert, Varghelovici). Schiff and Ioffe recommended a 0.5-1% water solution of copper sulfate in a dose of 25 drops three times a day for hypochromic anemia. Sh. B. Babayev, I. G. Priyev and M. G. Mirzakarimov successfully prescribed the salts of cobalt, copper and manganese in combination with iron in a dose of 5 mg each for victims of posthemorrhagic anemia. In order to avoid dyspeptic symptoms and a metallic taste it is recommended that the mixture of trace elements be administered in two doses together with milk. The forming caseinates of the metals are absorbed more easily than an aqueous solution of the salts. The daily hemoglobin increment attains 1-1.3 unit.

In the case of normal-hyporegenerative anemia, especially of the iron-refractory type, there is justification for administering hemostimulating

biotics in combination with prednisolone. Its use is attributable to the synergism of humoral factors: a hormone and erythropoietin forming under the influence of cobalt. In patients retaining a regenerative capacity of the bone marrow, over a period of two to three weeks the red blood indices are normalized. The number of leukocytes and thrombocytes does not change. The effectiveness of treatment in the case of hyporegenerative anemia is determined to a large extent by the course of the main disease. In victims of postinfectious, splenogenic, hypoplastic and sidero-achrestic anemias in some cases it is possible to observe an increase in the index of maturing of normoblasts in the bone marrow, an increase in the number of erythrocytes and the quantity of hemoglobin. A favorable effect of trace elements is noted in some patients with leukoses during the period of cytostatic therapy (V. Ya. Shustov).

Pregnant women, for prevention of anemia, in addition to iron are prescribed a solution of cobalt, copper and manganese salts. Due to the low level of the trace elements in mother's milk it is desirable for its enrichment to recommend the administration of biotics to nursing mothers. This makes it possible to ensure normal development of the child and is one of the effective means for preventing anemia in children of nursing age (V. A. Leonav, O. G. Kopytkova).

A condition for the effectiveness of trace elements is adequate iron content in the body and the retention of at least small centers of erythropoiesis in the bone marrow. During posthemorrhagic, postnatal and achylous chloranemia the iron entering the body in food or medicine, as a result of the hemostimulating effect of biotics, is mobilized more rapidly for hemoglobin synthesis; the formation of erythrocytes is also accelerated. In victims of infectious, tumorous, sidero-achrestic,

hypoplastic and iron-refractory anemias of different kinds the utilization of the "passive construction material," iron, available in the body is inhibited or interrupted. The trace elements favor the elimination of this unusual "block" in the reticulo-histiocytic system. It must be taken into account that under the influence of cobalt and copper a dissociated hemopoiesis may be established, when as a result of the relative iron inadequacy the hemoglobin level increases to a lesser degree than the number of erythrocytes and hypochromia develops. In order to preclude this, in such cases it is recommended that macro- and microelements be administered simultaneously. The optimum daily dose of cobalt for peroral administration is 15 mg, for copper - 10 mg, for manganese - 5 mg. Large doses exceeding the optimum doses by a factor of 10 are ineffective and can cause side effects.

In order to increase the biological activity of the trace elements a number of complex organometallic drugs have been created. These include vitamin B_{12}, coamide, cobalt-13, fercoven, ferrocobalt, cobaltamine, cobaltine, hemostimulin, ferrocupron, ferronavin, cofermin, etc. All of them, other than hemostimulin (internally), are administered parenterally.

One of the important additional methods for preventing anemia and treating patients may be prescription of a diet with a high content of cobalt, copper and manganese in a number of foods. The richest sources of trace elements in foods are beets, radishes, cabbage, vegetables, strawberries, oranges, mushrooms, beans, wheat and rice bran, oat and buckwheat groats, corn, liver and fish.

Thus, cobalt, copper and manganese can be prescribed for victims of

anemia in the form of salts of metals and organometallic complexes, as well as in food. The hemopoietic effect and harmlessness of trace elements are obvious. This is confirmed by a "massive experiment" with the use of biotic substances within the framework of a complex (substitutive or stimulating) antianemic therapy.

The work on trace elements in hematology is only beginning. This review familiarizes the reader with the results already attained in this field and makes it possible to glance into the future.

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